

The effect of endocrine responsiveness on high-risk breast cancer treated with dose-intensive chemotherapy: results of International Breast Cancer Study Group Trial 15-95 after prolonged follow-up

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Background: The role of adjuvant dose-intensive chemotherapy and its efficacy according to baseline features has not yet been established.

Patients and methods: Three hundred and forty-four patients were randomized to receive seven courses of standard-dose chemotherapy (SD-CT) or three cycles of dose-intensive epirubicin and cyclophosphamide (epirubicin 200 mg/m² plus cyclophosphamide 4 mg/m² with filgrastim and progenitor cell support). All patients were assigned tamoxifen at the completion of chemotherapy. The primary end point was disease-free survival (DFS). This paper updates the results and explores patterns of recurrence according to predicting baseline features.

Results: At 8.3-years median follow-up, patients assigned DI-EC had a significantly better DFS compared with those assigned SD-CT [8-year DFS percent 47% and 37%, respectively, hazard ratio (HR) 0.76; 95% confidence interval 0.58–1.00; *P* = 0.05]. Only patients with estrogen receptor (ER)-positive disease benefited from the DI-EC (HR 0.61; 95% confidence interval 0.39, 0.95; *P* = 0.03).

Conclusions: After prolonged follow-up, DI-EC significantly improved DFS, but the effect was observed only in patients with ER-positive disease, leading to the hypothesis that efficacy of DI-EC may relate to its endocrine effects. Further studies designed to confirm the importance of endocrine responsiveness in patients treated with dose-intensive chemotherapy are encouraged.

Key words: adjuvant treatment, dose-intensive chemotherapy, early breast cancer, endocrine responsiveness

introduction

The value of high-dose chemotherapy to treat breast cancer remains an open question, and in fact conflicting results are reported in the literature. Two studies showed significant prolonged disease-free survival (DFS) [1, 2]; others showed only a nonsignificant trend to improved DFS [3, 4] and others failed to show any advantage for high-dose chemotherapy [5–7].

Potential limitations of available data include inadequate patient selection, limited duration of follow-up and the heterogeneity of regimens used. Mature studies were designed in an era when adjuvant therapies were selected according to risk factors: the higher the risk the more intensive the treatment. Factors predictive of response, such as hormone receptor expression for predicting response to endocrine therapies, have become important in the selection of adjuvant treatment of breast cancer [8]. Breast cancer is now recognized as a heterogeneous disease in which the chance that one treatment program will benefit all is not realistic [9].

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Moreover, only a minority of published studies have been reported with a median follow-up exceeding 5 years, yet such prolonged follow-up is particularly important for the assessment of delayed events seen among patients with endocrine-responsive disease [10].

Finally, these studies used different strategies to increase the dose of chemotherapy administered. Most delivered a single course of myeloablative treatment with progenitor cell support as consolidation after multiple initial cycles of conventional dose chemotherapy [1, 3, 4]. Alternatively, in other studies dose-intensive chemotherapy was given from the start of treatment in order to have the best chance of killing relatively resistant cancer cells [2].

In 1995, the International Breast Cancer Study Group (IBCSG) initiated a clinical trial (Trial 15-95) to examine the role of dose-intensive epirubicin and cyclophosphamide (DI-EC) versus conventional adjuvant chemotherapy for patients with high-risk early breast cancer [11]. Here, we report mature results for women enrolled in IBCSG Trial 15-95 overall and examine selected predictive features in order to identify patients who might benefit from dose-intensive chemotherapy.

methods

study design

From July 1995 to March 2000, 344 premenopausal and young postmenopausal (≤ 65 years old) patients with histologically proven, high-risk operable breast cancer were randomized to receive either standard-dose chemotherapy (SD-CT) or DI-EC within 6 weeks of surgery as previously reported [11]. Briefly, high-risk operable breast cancer was defined by one or more of the following: ≥ 10 involved axillary lymph nodes, estrogen receptor (ER)-negative tumors with five or more involved axillary lymph nodes, or operable T_3 tumors with five or more involved axillary lymph nodes. ER status was determined by immunohistochemistry in most cases (88%) and otherwise by ligand-binding assay. Tumors were classified as ER negative based on an immunohistochemical (IHC) quantitative result of $<1\%$ stained cells, an IHC qualitative assay result of 'negative' or 'borderline' or ligand-binding assay of <10 fmol/mg of cytosol protein. The intention to carry out separate analyses according to ER status was originally specified in the protocol.

SD-CT consisted of i.v. injections of doxorubicin 60 mg/m² or epirubicin 90 mg/m² and cyclophosphamide 600 mg/m² (AC or EC, respectively) every 3 weeks for four cycles. This was immediately followed by 'classical' CMF comprising oral cyclophosphamide 100 mg/m² daily for 14 days and i.v. injections of methotrexate 40 mg/m² and fluorouracil 600 mg/m² on days 1 and 8 every 4 weeks for three cycles. DI-EC consisted of epirubicin 200 mg/m² i.v. over 1 h on day 1 and cyclophosphamide 4 mg/m² on day 2, given as 1 mg/m² i.v. over 30 min in four divided doses. DI-EC was given every 3 weeks for three cycles. Once chemotherapy had finished, all patients were assigned to receive tamoxifen 20 mg/day for 5 years.

Patients are being followed lifelong, with updates of disease and survival status required yearly. The median follow-up is 8.3 years.

statistical methods

DFS was defined as time from randomization to any breast cancer recurrence, a second primary malignancy, or death, whichever occurred first. Overall survival (OS) was defined as time from randomization to date of death from any cause. The Kaplan–Meier method was used to estimate survival distribution for DFS and OS [12]. The two-sided log-rank test was used to assess the statistical significance of treatment differences between

the survival distributions [13]. Univariate Cox proportional hazard models (with treatment effect only) were used to estimate the hazard ratios (HRs). Multivariate Cox models were carried out to detect the treatment effect considering the baseline characteristics [14]. The interaction of treatment and ER status cohorts was tested using a Cox model including treatment effect, ER status, and the interaction term.

Subpopulation treatment effect pattern plot (STEPP) analysis was used to investigate the pattern of differences in 5-year DFS percent between treatment arms according to patient age at study entry for ER-positive and ER-negative cohorts separately [15]. *P* values for the interaction tests of age and treatment groups were provided based on simulations.

A cumulative incidence analysis, with secondary malignancy and death without prior cancer events as competing events, was carried out to evaluate the treatment effects on time to breast cancer recurrence [16].

The incidence of amenorrhea was compared using Fisher's exact test. OS and DFS by the achievement of amenorrhea were tested using a landmark analysis [17] at 9 months. Time zero in the landmark analysis was chosen a priori at 9 months.

results

The Trial 15-95 population, selected to be at high risk for recurrence yet fit for dose-intensive therapy, consisted of relatively young patients (96% age < 60), mainly premenopausal (67%) and with disease that was predominantly ER negative (56%) (Table 1). Patients also tended to have high tumor burden (74% with ≥ 10 nodes positive, 70% tumor size > 2 cm) and high tumor grade 3 (59%). In the SD-CT group, 64% received epirubicin (EC) and the remainder received doxorubicin (AC).

DFS and OS

At 8.3-years median follow-up, patients assigned DI-EC showed a significantly better DFS than those assigned SD-CT (Figure 1A). The 8-year DFS percents were 47% and 37%, respectively, with the HR and 95% confidence interval of 0.76 [(0.58–1.00), *P* = 0.05] in favor of DI-EC. There was a nonsignificant trend favoring DI-EC in OS, with 75 deaths on DI-EC and 90 on SD-CT. The 8-year OS percents were 56% and 48%, respectively, with a HR of 0.76 [(0.56–1.03), *P* = 0.07] in favor of DI-EC (Figure 1B).

A multivariate analysis was carried out considering the baseline characteristics of age (< 40 versus ≥ 40), menopausal status, type of local surgery, ER status, tumor size, number of involved axillary nodes, and tumor grade. After adjusting for these covariates, there remained a trend in favor of DI-EC [DFS HR 0.78 (0.59–1.03), *P* = 0.08; OS HR 0.77 (0.56–1.05), *P* = 0.09].

sites of failure

Figure 2 presents the cumulative incidence of each of the competing causes of first DFS failure [breast cancer recurrence, secondary (non-breast) primary malignancy, or death without prior cancer event]. The significant effect of DI-EC on controlling breast cancer recurrence is evident (*P* = 0.01). More patients receiving DI-EC developed second primary malignancies (five in the DI-EC group and two in the SD-CT group, *P* = 0.19) or died without prior cancer events (four in the DI-EC group and one in the SD-CT group, *P* = 0.19).

Table 2 lists sites of first failure according to assigned treatment of all patients and according to ER status. A reduction in terms of events in favor of DI-EC was observed overall (54.3% versus 64.3%) and in the population with ER-positive disease (43%

versus 63%). A reduced number of distant metastases was observed among all patients assigned DI-EC (36.4% versus 49.1%) especially among patients with ER-positive disease (29.1% versus 45.7%).

Table 1. Patient characteristics

	SD-CT, n (%)	DI-EC, n (%)	Total, n (%)
Total cases	171	173	344
ER			
Negative	99 (58)	94 (54)	193 (56)
Positive	70 (41)	79 (46)	149 (43)
Unknown	2 (1)	0 (0)	2 (1)
Age (years)			
<40	39 (23)	44 (25)	83 (24)
40–59	123 (72)	125 (73)	248 (72)
≥60	9 (5)	4 (2)	13 (4)
Premenopausal	115 (67)	117 (67)	232 (67)
Postmenopausal	56 (33)	56 (33)	112 (33)
Mastectomy no RT	57 (33)	69 (40)	126 (37)
Mastectomy + RT	55 (32)	56 (32)	111 (32)
Breast conservation no RT	2 (1)	1 (1)	3 (1)
Breast conservation + RT	57 (34)	47 (27)	104 (30)
Positive nodes			
5–9	37 (22)	54 (31)	91 (26)
≥10	134 (78)	119 (69)	253 (74)
Tumor size (cm) ^a			
<2	45 (26)	59 (34)	104 (30)
2–5	91 (54)	84 (49)	175 (51)
>5	33 (19)	30 (17)	63 (18)
Tumor grade ^b			
1	5 (3)	12 (7)	17 (5)
2	60 (35)	64 (37)	124 (36)
3	106 (62)	95 (56)	201 (59)

^aTumor size unknown in two patients.

^bHistological grade unknown in two patients.

SD-CT, standard-dose chemotherapy; DI-EC, dose-intensive epirubicin and cyclophosphamide; ER, estrogen receptor; RT, radiation therapy.

DFS according to ER status

Figure 3 shows Kaplan–Meier curves of DFS for the ER-negative and ER-positive cohorts. For the ER-positive cohort, there was a significant benefit for the DI-EC group (the 8-year OS percents were 60% and 38%, respectively, with a HR of 0.61 [(0.39–0.95), $P = 0.03$]). By contrast, no treatment difference was observed for the ER-negative cohort for DFS (the 8-year OS percents were 37% and 37%, respectively, with a HR of 0.92 [(0.65–1.30), $P = 0.62$]), although the treatment-by-ER status interaction was not statistically significant ($P = 0.21$).

For ER-positive and ER-negative patients separately, a multivariate analysis was carried out on DFS allowing for the baseline characteristics of age (<40 versus ≥40), menopausal status, type of local surgery, tumor size, number of involved axillary nodes, and tumor grade. The results are shown in Table 3. A HR and 95% confidence interval of 0.54 [(0.34–0.87), $P = 0.01$] in favor of DI-CT was observed only in ER-positive disease.

amenorrhea and outcome

Information on menses was collected at baseline and every 3 months for the first 2 years, then every 6 months. Women were classified as achieving amenorrhea if they reported no menses during months 7 through 9 from randomization. A total of 193 patients were assessable and included in this analysis. The achievement of amenorrhea in premenopausal patients was statistically higher for DI-EC compared with SD-CT (92.6% versus 77.6%, $P = 0.004$). The magnitude of the effect was larger in patients aged <40 years, in whom it was 85.4% versus 50.0% overall, and 93.8% versus 57.1% and 80% versus 45% in the cohorts of patients with ER-positive and ER-negative disease, respectively.

No amenorrhea effects were detected on DFS and OS in this landmark analysis either in all patients or subgroups of patients defined by ER status and age (data not shown). However,

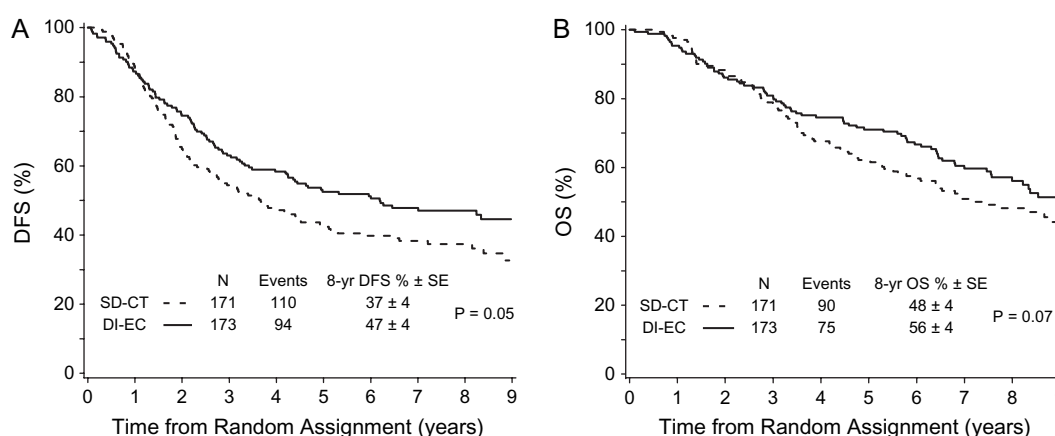


Figure 1. Disease-free survival (DFS) (A) and overall survival (B) comparing patients assigned to dose-intensive epirubicin and cyclophosphamide × 3 (DI-EC) with patients assigned to standard-dose chemotherapy (SD-CT). The median follow-up was 8.3 years.

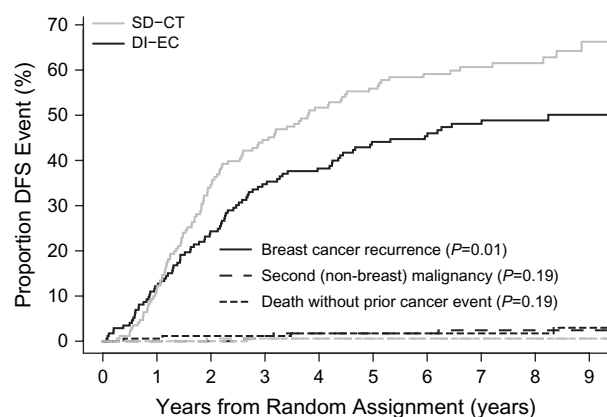


Figure 2. Cumulative incidence of competing causes of failure according to treatment.

among the 88 ER-positive patients, the group in which we expected to see the amenorrhea effect, 77 (87.5%) achieved amenorrhea, while only 11 (12.5%) did not, therefore limiting the power to detect any amenorrhea-related effect.

DFS according to age within ER cohorts

The STEPP analysis in Figure 4 shows 5-year DFS percent for DI-EC and SD-CT groups in overlapping subpopulations defined by age at study entry, for ER-positive and ER-negative cohorts, for all patients and for patients with ≥ 10 axillary lymph nodes positive. Due to the small number of patients, the STEPP plots showed large variability. Both ER-positive and ER-negative cohorts randomized to DI-EC showed higher 5-year DFS percent than those randomized to SD-CT, except in older patients. Younger patients (age < 40) with ER-positive disease appeared to benefit most from DI-EC, but the interaction of age and treatment was not statistically significant ($P = 0.54$).

discussion

IBCSG Trial 15-95 is one of the few trials designed to compare immediate multiple cycle dose-intensive chemotherapy with standard-dose adjuvant chemotherapy. The results illustrate that the average effect observed in the trials overall may be the result of different treatment effects in different subpopulations. Moreover, although a prolonged follow-up is required in order to properly address the role of relapses in the endocrine-responsive population [10], few studies available in the literature report prolonged observation. Here, we present results after a prolonged follow-up (8.3 years).

On average, DI-EC had a significantly better DFS compared with SD-CT, supporting the role of dose-intensive chemotherapy in the adjuvant therapy of high-risk breast cancer. However, our results suggest a different pattern of outcome according to the degree of potential endocrine responsiveness, in that the benefit from DI-EC was evident only among the cohort of patients with ER-positive tumors.

Several other clinical studies have provided evidence of different interactions of chemotherapy with cellular growth according to ER status. Studies of the therapeutic benefit of

Table 2. Sites of first treatment failure

	SD-CT, n (%)	DI-EC, n (%)	Total, n (%)
All patients	171	173	344
Total failures	110 (64.3)	94 (54.3)	204 (59.3)
Total deaths from any cause	90 (54.6)	75 (45.5)	165 (48.0)
Sites of first failure			
Local	9 (5.3)	10 (5.8)	19 (5.5)
Contralateral \pm local	2 (1.2)	4 (2.3)	6 (1.7)
Regional \pm above	11 (6.4)	6 (3.5)	17 (4.9)
Distant \pm above	84 (49.1)	63 (36.4)	147 (42.7)
Soft tissue \pm above	5 (2.9)	5 (2.9)	10 (2.9)
Bone \pm above	29 (17.0)	12 (6.9)	41 (11.9)
Viscera \pm above	50 (29.2)	46 (26.6)	96 (27.9)
Second (non-breast) malignancy	2 (1.2)	5 (2.9)	7 (2.0)
Death without prior cancer event	1 (0.6)	4 (2.3)	5 (1.5)
Unknown	0 (0)	1 (0.6)	1 (0.3)
ER-positive cohort	70	79	149
Total failures	42 (60.0)	34 (43.0)	76 (51.0)
Total deaths from any cause	32 (45.7)	22 (27.9)	54 (36.2)
Sites of first failure			
Local	2 (2.9)	4 (5.1)	6 (4.0)
Contralateral \pm local	1 (1.4)	2 (2.5)	3 (2.0)
Regional \pm above	5 (7.1)	0 (0)	5 (3.4)
Distant \pm above	32 (45.7)	23 (29.1)	55 (36.9)
Soft tissue \pm above	2 (2.9)	0 (0)	2 (1.3)
Bone \pm above	12 (17.1)	5 (6.3)	17 (11.4)
Viscera \pm above	18 (25.7)	18 (22.8)	36 (24.2)
Second (non-breast) malignancy	1 (1.4)	3 (3.8)	4 (2.7)
Death without prior cancer event	1 (1.4)	1 (1.3)	2 (1.3)
ER-negative cohort	99	94	193
Total failures	67 (67.7)	60 (63.8)	127 (65.8)
Total deaths from any cause	58 (58.6)	53 (56.4)	111 (57.5)
Sites of first failure			
Local	7 (7.1)	6 (6.4)	13 (6.7)
Contralateral \pm local	1 (1.0)	2 (2.1)	3 (1.6)
Regional \pm above	5 (5.1)	6 (6.4)	11 (5.7)
Distant \pm above	52 (52.5)	40 (42.6)	92 (47.7)
Soft tissue \pm above	3 (3.0)	5 (5.3)	8 (4.1)
Bone \pm above	17 (17.2)	7 (7.4)	24 (12.4)
Viscera \pm above	32 (32.3)	28 (29.8)	60 (31.1)
Second (non-breast) malignancy	1 (1.0)	2 (2.1)	3 (1.6)
Death without prior cancer event	0 (0)	3 (3.2)	3 (1.6)
Unknown	0 (0)	1 (1.1)	1 (0.5)

SD-CT, standard-dose chemotherapy; DI-EC, dose-intensive epirubicin and cyclophosphamide.

ovarian function suppression by cytotoxic agents have yielded controversial results, possibly related to the large variation in chemotherapy dose intensity and duration as well as to different patient characteristics [18–21]. Recently, however, two randomized trials showed statistically significant increases in

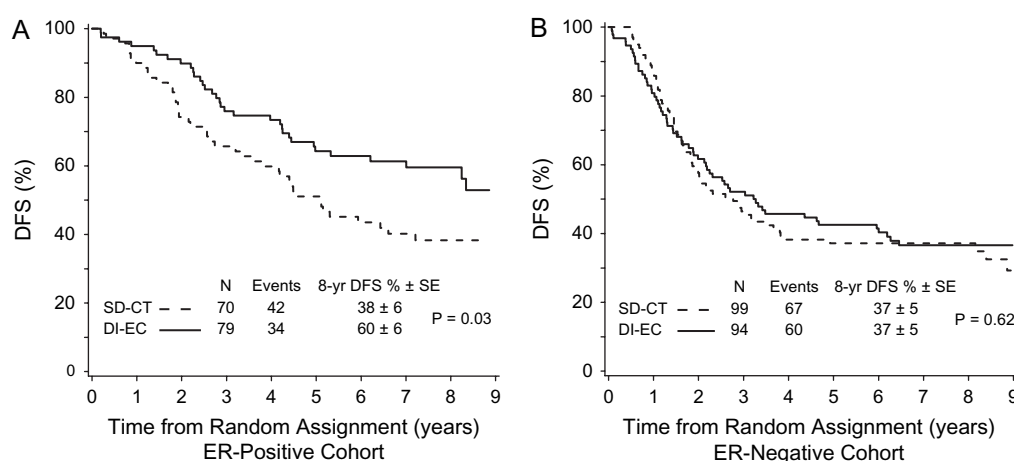


Figure 3. Disease-free survival (DFS) for estrogen receptor (ER)-positive (A) and ER-negative cohorts (B) comparing patients assigned to dose-intensive epirubicin and cyclophosphamide \times 3 (DI-EC) with patients assigned to standard-dose chemotherapy (SD-CT).

both the incidence of amenorrhea and DFS for very young patients (those aged 39 years or younger) with ER-positive tumors who received 6 months of standard-dose chemotherapy [22, 23]. In addition, results of a large National Surgical Adjuvant Breast and Bowel Project (NSABP) trial (B-30) indicated that prospectively studied amenorrhea was associated with improved DFS and OS irrespective of the type of chemotherapy used [24]. The incidence of amenorrhea was meticulously studied in Trial 15-95, and we found that achieving amenorrhea was significantly higher in patients who received DI-EC, particularly among patients aged <40 years. A STEPP analysis, conducted in order to ascertain the magnitude of the effect of DI-EC in patients with ER-positive tumors according to age, showed a visual trend suggesting a larger effect for DI-EC in younger patients (Figure 4), therefore supporting a possible correlation between the achievement of ovarian function suppression and efficacy of DI-EC.

Other studies exploring the activity of high-dose chemotherapy described a more pronounced effect of high-dose chemotherapy in younger patients [25] and in those with disease features typical of endocrine-responsive disease (e.g. low grade and HER2-negative disease) [26], although precise analyses according to endocrine responsiveness, menstrual status, type of treatment, and outcome are seldom available. In these studies, the delayed time course of improved DFS in patients treated with high-dose chemotherapy was reminiscent of that observed with endocrine treatments.

Cytotoxic therapy may have an endocrine effect in postmenopausal women through suppression of adrenal function [27] perhaps partly due to increased supportive use of corticosteroids.

The West German Study Group (WSG) AM-01 trial used, as the present study, an early multiple cycle dose intensification strategy in adjuvant therapy of breast cancer [2]. Their phase III trial compared a dose-dense chemotherapy regimen with an up front epirubicin-based double high-dose chemotherapy regimen in 403 patients with early breast cancer. After a median follow-up of 48.6 months, the 4-year event-free survival (intention-to-treat analysis) was 60% (95% CI 53%–67%) in the high-dose chemotherapy group and 44% (37%–52%) in the

Table 3. DFS according to ER status

Parameter	Multivariate Cox model results		
	Hazard ratio	95% CI	P value
ER-positive cohort			
DI-EC versus SD-CT	0.54	0.34–0.87	0.01
Age <40 versus \geq 40 years	0.84	0.45–1.57	0.59
Postmenopausal versus premenopausal	1.31	0.75–2.29	0.35
Mastectomy + RT versus breast conservation	1.68	0.86–3.31	0.13
Mastectomy no RT versus breast conservation	2.62	1.38–4.97	0.003
Tumor grade ^a	1.14	0.77–1.69	0.52
Number of involved axillary nodes ^a	1.01	0.99–1.04	0.31
Tumor size ^a	1.09	0.98–1.21	0.10
ER-negative cohort			
DI-EC versus SD-CT	0.91	0.64–1.30	0.60
Age <40 versus \geq 40 years	1.03	0.67–1.60	0.88
Postmenopausal versus premenopausal	0.88	0.58–1.35	0.57
Mastectomy + RT versus breast conservation	1.12	0.68–1.84	0.65
Mastectomy no RT versus breast conservation	1.14	0.73–1.78	0.57
Tumor grade ^a	1.07	0.75–1.54	0.71
Number of involved axillary nodes ^a	1.03	1.01–1.05	0.01
Tumor size ^a	1.00	0.92–1.09	0.96

^aTumor grade, number of involved axillary nodes, and tumor size were included in the model as continuous variables.

DFS, disease-free survival; ER, estrogen receptor; CI, confidence interval; DI-EC, dose-intensive epirubicin and cyclophosphamide; SD-CT, standard-dose chemotherapy; RT, radiation therapy.

control group ($P = 0.00069$). Retrospective subgroup analyses showed benefit from high-dose chemotherapy independent of hormone receptor status and age. Effects were more

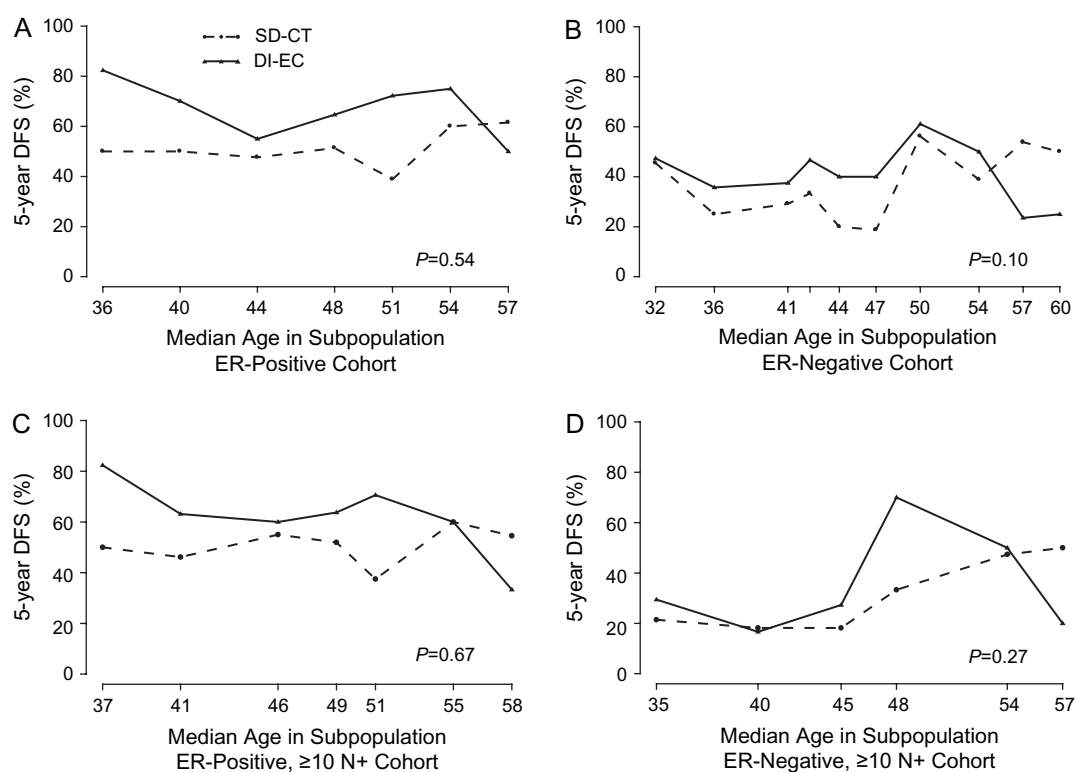


Figure 4. Subpopulation treatment effect pattern plots (STEPPs) for overlapping age subgroups. The 5-year disease-free survival (DFS) percentages are plotted for cohorts defined by estrogen receptor status (positive, left; negative, right) among all patients (A and B) and patients with ≥ 10 positive nodes (C and D).

pronounced in young patients, but no data are available on the effect according to age, amenorrhea in endocrine-responsive disease, and in those with hormone receptor-negative disease. A subsequent analysis carried out on paraffin-embedded tumors from 236 patients confirmed a superior efficacy of high-dose therapy in the subgroup of triple-negative and/or grade 3 tumors [28]. The difference between this effect and our observations of superior efficacy among patients with ER-positive disease may be related to the difference in the conventional arm used, which comprised a dose-dense regimen used for ~ 3 months. This treatment duration may be suboptimal in patients with endocrine-non-responsive disease [29].

A recent meta-analysis of individual patient data from 15 randomized adjuvant breast cancer trials including 6210 patients [30] showed that after a median follow-up of 6 years, high-dose chemotherapy significantly prolonged DFS (HR 0.87; 95% CI 0.81–0.94; $P = 0.0001$). After adjusting for steroid hormone receptor content in the subgroup of patients for whom it was available, a significant DFS benefit for high-dose chemotherapy (HR 0.83; 95% CI 0.77–0.90; $P < 0.0001$) was observed with no reported interaction between steroid hormone receptors and treatment of DFS. Several factors may explain the different results achieved in the meta-analysis if compared with the present study. The meta-analysis estimates of the average magnitude of treatment effect are derived from a mixture of evidence that combines the results of different patients treated with different therapies and with a large variation in the follow-up duration. Moreover, no

results are available according to menopausal status, and no information was reported on the methods and cut-offs used in the various studies for the determination of selected prognostic factors (e.g. steroid hormone receptors).

A potential limitation of the present trial is the decision (made in the early 1990s) to use tamoxifen in all patients including those with ER-negative disease. We have data from unplanned exploratory analyses of other trials suggesting that tamoxifen administered sequentially after adjuvant chemotherapy may have a detrimental effect on patients with ER-absent tumors (HR 2.10; 95% CI 1.03–4.29; $P = 0.04$) [22]. It is therefore possible that a detrimental interaction effect of tamoxifen with chemotherapy may have reduced any possible advantage for DI-EC in patients with ER-negative disease in our study.

The DI-EC treatment is clearly more toxic, with nearly all patients experiencing grade 4 neutropenia and thrombocytopenia, more time spent in the hospital, and four treatment-related deaths [11]. As reported in the companion quality-of-life study, patient's self-reported detrimental effects of quality of life were limited to the 3-month treatment period, and recovery was sooner than on SD-CT [31]. However, reliable evidence of benefit is required to justify the burden and expense of dose-intensive therapy. We did not observe any benefit for patients with ER-negative disease, and the results in patients with ER-positive disease raise the hypothesis that efficacy of DI-EC may relate to its endocrine effects. There are less costly ways of offering endocrine therapy for patients with endocrine-responsive disease.

In conclusion, the results of Trial 15-95 indicate that DI-EC improved DFS although the benefit was largely dependent on the endocrine responsiveness of the tumor. Despite the impressive magnitude of the effect of DI-EC associated with endocrine responsiveness, the compelling biological explanations for this effect, and the balance between groups with respect to prognostic factors, the potential for bias still exists due to the retrospective nature of the evaluation and the sample size of the study. Similar observations by several studies represent a strong incentive to improve further analyses by requiring more accurate and reliable assessments of tumor and patient characteristics. If confirmed, patients with endocrine-non-responsive disease would benefit most from trials of molecularly targeted treatments, many of which act synergistically with cytotoxic agents.

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